

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The manuscript then underwent further review at BMJ Open and was accepted after further revisions.

## ARTICLE DETAILS

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| <b>TITLE (PROVISIONAL)</b> | The apparent breastfeeding paradox in very preterm infants: relationship between breastfeeding, early weight gain, and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT  |
| <b>AUTHORS</b>             | Jean-Christophe Rozé, Dominique Darmaun, Clair-Yves Boquien, Cyril Flamant, Jean Charles Picaud, Christophe Savagner, Olivier Claris, Alexandre Lapillonne, Delphine Mitanchez, Bernard Branger, Umberto Simeoni, Monique Kaminski and Pierre-Yves Ancel |

## REVIEWS FOR BMJ

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| <b>REVIEWER</b>        | Anthony Williams, St George's, University of London |
| <b>REVIEW RETURNED</b> | 20/10/2011  |

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| <b>GENERAL COMMENTS</b> | <p>This is an interesting paper which draws attention to disparate effects of breastfeeding on the early ponderal growth of preterm infants and their subsequent neurological development. The analysis performed uses data from two large French preterm birth cohorts born six years apart. As the authors point out hospital nutritional practices may have changed over this interval, and possibly this explains differing relationships between growth in hospital and neurodevelopmental outcome observed in each. There could, however, be other explanations since different methods of neurodevelopmental assessment were applied at different ages.</p> <p>The area that the authors have attempted to study is an extremely difficult one. It is important to appreciate that one is necessarily dependent on observational data in this field of enquiry since it would be unethical to allocate preterm infants at random to breastfeeding. In their discussion the authors clearly set out their appreciation of the biases and confounders inherent in this topic and Table 1 shows the large number of sociodemographic, neonatal phenotypic and treatment variables that are associated with breastfeeding at discharge. The authors have "adjusted" for these using a "breastfeeding propensity score". This is not an approach I know but appropriate citations have been included. Despite these I do not think the nature of this score is explained sufficiently clearly for the reader as different contributors to the models applied are mentioned at various points in the manuscript. For example page 5 suggests that birthweight z-score and gestational age were used in the calculation of "propensity score" but at other points there is mention of adjusting for "propensity score", gestational age and birthweight z-score together (e.g. pages 8 and 9). Confusingly birthweight z-score is also used to calculate in-hospital weight gain (as difference birth and discharge z-score) which is then</p> |
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|  | <p>“....adjusted for” [amongst other things] birthweight z-score and propensity score (Table 4).</p> <p>A couple of more minor points:</p> <ul style="list-style-type: none"> <li>• I think the authors should be more specific in their use of the word “growth” when by and large they mean “weight gain”. Although it has widespread clinical currency as a day-to-day measure the latter is of course a poor descriptor of changes in body composition and metabolic function accompanying growth, let alone brain growth. When viewed from this perspective the authors may find their findings less of a “paradox”.</li> <li>• The term “postconceptional age” (figure 2) is variously used and “corrected age” (which is I think what the authors mean) has gained more widespread acceptance (see Engle WA. Age terminology during the perinatal period. Pediatrics 2004;114:1362-4.)</li> </ul> <p>In summary, this is an interesting paper which makes a provocative point of much clinical relevance (viz. that weight gain is a poor predictor of developmental outcome in the breastfed preterm baby) but the statistical modelling employed is complex and requires close examination. The variables used in adjustment may not be entirely independent either of each other or of the outcome (in the case of weight gain). This could be more clearly explained to the reader.</p> |
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| <b>REVIEWER</b>        | Dharmapuri Vidyasagar, University of Illinois, Chicago |
| <b>REVIEW RETURNED</b> | 15/12/2011   |

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| <b>GENERAL COMMENTS</b> | <p>The aims of the study were to assess the complex relationship of BF at discharge with growth and development. The investigators hypothesized that sub-optimal nutrition in NICU is associated with later poor cognitive function. The investigators studied the growth pattern of very preterm infants who were breastfed during their stay in the hospital (NICU) and then after discharge and assessed their development at 2-5 years of life. During the hospital stay breastmilk feeding was supplemented with fortifiers but not after discharge (this is one of the variables that needs close analysis; how much, caloric density etc.) They compared the weight changes during and after discharge using Z scores. In addition they also measured the changes in head circumference.</p> <p><b>MATERIAL AND METHODS:</b></p> <p>The population included in this study was from two different studies from two different periods. The EPIPAGE study and the LIFT study. EPIPAGE study included infants born between 22 and 32 weeks of gestation in 1997 who survived (n=2282), For developmental assessment infants whose status regarding breastfeeding at time of discharge was known (n=2163) were included in this study, In this group the neuropsychological assessment was performed using the Kaufman Assessment Battery for Children (K-ABC) at five years of age . This scale is standardized to a mean of 100 (SD 15). An MPC in the lower tercile (score of less than 85) was considered as an index of suboptimal neurodevelopment</p> <p>In LIFT cohort 1733/1857 surviving babies with gestational age less than 33 weeks born between , 2003 and 2008 those whose status regarding breastfeeding at time of discharge was known. In this Cohort, neuron-developmental assessment was performed using age and stages questionnaires (ASQ), a questionnaire completed by parents at a corrected age of two years. They compared growth</p> |
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pattern in the NICU with later developmental quotients in both groups. Propensity Score was calculated in each cohort to find the differences in both cohorts that may influence the growth pattern during the hospital stay and after discharge. Variables significantly associated with breastfeeding at discharge were very similar in both cohorts.

#### MAJOR FINDINGS.

In both cohorts, breastfeeding was associated with a significant reduction of risk for a suboptimal neurodevelopmental assessment at 2 years of corrected age (LIFT cohort) and at 5 Years, in EIPAGE cohort.

Breastfeeding was associated with an increased risk of losing one weight Z-Score during NICU stay

(Correction on line 46 in NOT in hospitalization)?

Growth during neonatal hospitalization, exposure to breastfeeding, and neurodevelopment

This is the most important findings of the study. During hospitalization restricted growth (i.e., lower birth weight Z score) was associated before and after adjustment for gestational age and sex with later suboptimal neurodevelopmental assessment in both cohorts.

Page 9 line 15-21 the statement says : "After adjustment for weight Z Score at birth, sex and propensity score, breastfeeding at discharge was significantly associated to an increased risk of having a head circumference Z-score higher than 0.5 at five years in EIPAGE cohort, (n=1412, aOR=1.47,[1.10-1.95]) and at two years of corrected age in LIFT cohort"

It is an advantage rather than a risk !

**STRENGTHS OF THE STUDY:** The study includes large population data from two different cohorts at different times. Large proportion of population included in follow up study. Good statistical analysis

#### WEAKNESSES:

1. Propensity score enables better comparison between the cohorts and groups however the calculation of PROPENSITY score did not include important variables that affect weight gain in the NICU e.g. time taken to start oral feeds, duration of hyperalimentation, lack of uniform protocols in regard to initiation of oral/tube feeding.

Particularly there was no attempt to calculate the caloric intake during NICU stay

2. It is an observational study hence associated deficiencies

3. No explanation for the mechanism. Although difficult to pin point, authors should provide possible mechanisms e.g. better bonding, better care given by parents

There are a few minor typographical errors: page 10, line 47

LIKELY, Line 49 CAN

#### COMMENTS

The main findings of the study are that in both independent cohorts of preterm infants studied, breastfeeding at discharge (continuation of breast feeding after discharge? ) was associated with a reduction in the risk for a suboptimal neurodevelopmental assessment at two or five years of age despite a higher risk for suboptimal growth (loss

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|  | <p>of one weight Z-Score) during neonatal hospitalization in these breastfed infants. They define these findings as “breastfeeding paradox”, meaning that breast feeding in the NICU was associated with poor weight gain but continuation of breast feeding after discharge was associated with better neurodevelopmental outcome at 2 and 5 years of age in very preterm infants. These findings are of critical importance and provide strong evidence for breast feeding in extreme premature infants both during NICU stay and after discharge.</p> <p>It is agreed that taken all data from literature and current study there is a consistence benefit of BF on later neuro development. And it provides evidence to encourage mothers who wish to breast feed, ( Page 11 Lines 12-20 ...)</p> <p>However calling it a “Breastfeeding Paradox” is debatable. What is the paradox? Loss of weight by one Z score during hospital stay can be well explained independent of breast feeding. Suboptimal growth in extreme premature babies In the NICU is well recognized even in the formula fed infants . Such suboptimal growth is due to difficulties in delivering optimal calories to sick VLBW infants: illness, limitation of feeding, fluid intake and associated physiological constraints that affect nutritional intake in this population. However the beneficial effects of breast feeding on neurodevelopment developmental outcome are well recognized and the findings of this study confirm previous studies.</p> <p>My argument against the use of the term “Breast Feeding Paradox” is that it implies that breast feeding in NICU is THE CAUSE for low birth weight z scores. There are several factors that influence the weight growth in THE NICU which may adversely influence the growth of very preterm infants. As the investigators found that there was no association between NICU postnatal growth and developmental findings at 5 yrs.(p 8 line 55-60). Because nutrition was better in LIFT cohort . This again suggests that breast feeding is NOT the only cause low weight gain during the NICU stay. The study strengthens the concept that moms should be Advised to continue breast feeding of very premature babies after discharge from NICU.</p> |
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## VERSION 1 – AUTHOR RESPONSE

### Answers to Reviewer 1

# BMJ.2011.001225.R1 entitled "The Breastfeeding paradox in very preterm infants"

We appreciate Reviewer 1's insightful comments. In the following, excerpts from the Reviewer's comments are shown in italics, and immediately followed by our answers in Arial font.

#### *Comments:*

*This is an interesting paper which draws attention to disparate effects of breastfeeding on the early ponderal growth of preterm infants and their subsequent neurological development. The analysis performed uses data from two large French preterm birth cohorts born six years apart. As the authors point out hospital nutritional practices may have changed over this interval, and possibly this explains differing relationships between growth in hospital and neurodevelopmental outcome observed in each. There could, however, be other explanations since different methods of neurodevelopmental*

assessment were applied at different ages.

**Answer:** We agree with the Reviewer's comment. LIFT is an open, ongoing cohort: the population is followed until 5 years of age, and evaluation was complemented with an assessment of school performance by school teachers during the 6<sup>th</sup> year of life in kindergarten. Only a fraction of patients enrolled in LIFT cohort had reached 5 years when the study was performed. In the patients who reached 5 years, a very good correlation between 2-yrs ASQ and school performance as well as IQ was observed (unpublished data, manuscript in preparation). We therefore think the evaluation of neurodevelopment using ASQ is reliable.

*The area that the authors have attempted to study is an extremely difficult one. It is important to appreciate that one is necessarily dependent on observational data in this field of enquiry since it would be unethical to allocate preterm infants at random to breastfeeding. In their discussion the authors clearly set out their appreciation of the biases and confounders inherent in this topic and Table 1 shows the large number of sociodemographic, neonatal phenotypic and treatment variables that are associated with breastfeeding at discharge. The authors have "adjusted" for these using a "breastfeeding propensity score". This is not an approach I know but appropriate citations have been included. Despite these I do not think the nature of this score is explained sufficiently clearly for the reader as different contributors to the models applied are mentioned at various points in the manuscript. For example page 5 suggests that birthweight z-score and gestational age were used in the calculation of "propensity score" but at other points there is mention of adjusting for "propensity score", gestational age and birthweight z-score together (e.g. pages 8 and 9). Confusingly birthweight z-score is also used to calculate in-hospital weight gain (as difference birth and discharge z-score) which is then "...adjusted for" [amongst other things] birthweight z-score and propensity score (Table 4).*

**Answer:** We agree with the Reviewer's comment, we clearly run a risk of "over adjustment". After extensive discussion we nevertheless decided to calculate the risk of non optimal neurodevelopmental outcome, with adjustment for sex, gestational age and birthweight z-score together because neurodevelopment and weight gain are closely influenced by these 3 variables. As we were concerned about the risk of an under adjustment, and as recommended by D'Agostino (Statistics in Medicine, 1998, 17 : 2265-2281) we decided to adjust for variable closely associated with outcome, even though the variables are already included in the calculation of propensity score. This point is now specified (gestational age and birth weight Z-score Due to the known relationship between gestational age, weight gain and suboptimal development, these variables were included as confounding factors in the multivariable model even if they are already included in the calculation of propensity score, as suggested by other authors) in the text in the revised manuscript (page 6, lines 12).

Nevertheless, we calculated adjusted OR with adjustment either (a) for propensity score only; or (b) for propensity score plus sex, gestational, age and birth weight Z-Score. We observed very similar aOR with both approaches :

| RISK OF NON OPTIMAL OUTCOME | OR adjusted for propensity score only | OR adjusted for propensity score, sex, birth weight Z-score, and GA |
|-----------------------------|---------------------------------------|---|
| In EPIPAGE cohort:          | OR = 0.65 (0.47-0.89)                 | OR = 0.65 (0.47-0.89)   |
| In LIFT cohort              | OR = 0.64 (0.45-0.88)                 | OR = 0.63 (0.45-0.87)   |

*A couple of more minor points:*

- I think the authors should be more specific in their use of the word “growth” when by and large they mean “weight gain”. Although it has widespread clinical currency as a day-to-day measure the latter is of course a poor descriptor of changes in body composition and metabolic function accompanying growth, let alone brain growth. When viewed from this perspective the authors may find their findings less of a “paradox”.*

**Answer:** We replaced the term ‘growth’ with ‘weight gain’ throughout the manuscript when it was appropriate.

- The term “postconceptional age” (figure 2) is variously used and “corrected age” (which is I think what the authors mean) has gained more widespread acceptance (see Engle WA. Age terminology during the perinatal period. Pediatrics 2004;114:1362-4.)*

**Answer:** We made the requested correction in the revised manuscript.

*In summary, this is an interesting paper which makes a provocative point of much clinical relevance (viz. that weight gain is a poor predictor of developmental outcome in the breastfed preterm baby) but the statistical modelling employed is complex and requires close examination. The variables used in adjustment may not be entirely independent either of each other or of the outcome (in the case of weight gain). This could be more clearly explained to the reader.*

**Answer:** We agree with reviewer's comment. We attenuated our provocative message in the title and in the first and second paragraph of discussion. We now explain the term of apparent paradox by this sentence :

"Nevertheless, this paradox is probably only an apparent paradox because weight gain during hospitalization is a poor predictor of the quality of growth, as it does not provide any insight into the changes in body composition (page 8, line 31)

Similarly, we now state the limitations of the approach pointed out by Reviewer 1: " the variables used in adjustment may not be entirely independent either of each other or of the outcome" (page10, line 29)

## **Answers to Reviewer 2**

# BMJ.2011.001225.R1 entitled "*The Breastfeeding paradox in very preterm infants*"

We appreciate Reviewer 2's insightful comments. In the following, excerpts from the Reviewer's comments are shown in italics, and immediately followed by our answers in Arial font.

*Comments:*

*The aims of the study were to assess the complex relationship of BF at discharge with growth and development. The investigators hypothesized that sub-optimal nutrition in NICU is associated with later poor cognitive function. The investigators studied the growth pattern of very preterm infants who were breast fed during their stay in the hospital (NICU) and then after discharge and assessed their development at 2-5 years of life. During the hospital stay breast milk feeding was supplemented with fortifiers but not after discharge. (This is one of the variables that needs close analysis How much, caloric density etc.) They compared the weight changes during and after discharge using Z scores. In addition they also measured the changes in head circumference.*

**Answer:**\_\_The Reviewer is right, the information regarding how much fortifier was given would be helpful but is, unfortunately, not available in either database. This is addressed in the revised discussion (see 'Weaknesses' section, fifth paragraph of discussion) : "Moreover, how much fortifier was given could, unfortunately not be retrieved from either of the two databases". (page 10, line 31)

As stated in the manuscript, the loss of Z-score was less in the more recent LIFT cohort, suggesting a better use of fortifiers. Nevertheless, in each cohort, breastfeeding is associated with a greater loss of weight Z-score. This obviously is an association, and does not prove a causal relationship. However, we know for sure that fortification is most often discontinued as soon as suckling is felt / judged to be satisfactory, so as not to disturb suckling. This problem is at the very root of the current study.

## **MATERIAL AND METHODS:**

*Population included in this study was from two different studies from two two different periods : The EPIPAGE study and the LIFT study. EPIPAGE study included infants born between 22 and 32 weeks of gestation in 1997 who survived (n=2282), For developmental assessment infants whose status regarding breastfeeding at time of discharge was known (n=2163) were included in this study, In this group the neuropsychological assessment was performed using the Kaufman Assessment Battery for*

*Children (K-ABC) at five years of age . This scale is standardized to a mean of 100 (SD 15). An MPC in the lower tercile (score of less than 85) was considered as an index of suboptimal neurodevelopment*

*In LIFT cohort 1733/1857 surviving babies with gestational age less than 33 weeks born between , 2003 and 2008 those whose status regarding breastfeeding at time of discharge was known. In this Cohort, neuron-developmental assessment was performed using age and stages questionnaires (ASQ), a questionnaire completed by parents at a corrected age of two years. They compared growth pattern in the NICU with later developmental quotients in both groups. Propensity Score was calculated in each cohort to find the differences in both cohorts that may influence the growth pattern during the hospital stay and after discharge. Variables significantly associated with Breastfeeding at discharge were very similar in both cohorts.*

#### **MAJOR FINDINGS.**

*In both cohorts, breastfeeding was associated with a significant reduction of risk for a suboptimal neurodevelopmental assessment at 2 years of corrected age (LIFT cohort) and at 5 Years, in EPIPAGE cohort.*

*Breastfeeding was associated with an increased risk of losing one weight Z-Score during NICU stay (Correction on line 46 in NOT in hospitalization)?*

**Answer:** We agree. We made the correction

*Growth during neonatal hospitalization, exposure to breastfeeding, and neurodevelopment This is the most important findings of the study. During hospitalization restricted growth (i.e., lower birth weight Z score) was associated before and after adjustment for gestational age and sex with later suboptimal neurodevelopmental assessment in both cohorts.*

*Page 9 line 15-21 the statement says : "After adjustment for weight Z Score at birth, sex and propensity score, breastfeeding at discharge was significantly associated to an increased risk of having a head circumference Z-score higher than 0.5 at five years in EPIPAGE cohort, (n=1412, aOR=1.47,[1.10-1.95]) and at two years of corrected age in LIFT cohort" It is an advantage rather than a risk !*

**Answer:** We agree: achieving a higher Z-score in head circumference obviously is an advantage rather than an unwanted change: the term 'risk' was simply used, as commonly used by statisticians, with no reference to the desirability of the change observed . We now replaced 'risk' with 'chance' in the revised manuscript (page 8, line 14).

**STRENGTHS OF THE STUDY:** *The study includes large population data from two different cohorts at different times. Large proportion of population included in Follow up study. Good statistical analysis*

**Answer:** We appreciate the comment.

#### **WEAKNESSES:**

*1. Propensity score enables better comparison between the cohorts and groups however the calculation of PROPENSITY score did not include important variables that affect weight gain in the NICU e.g. time taken to start oral feeds, duration of hyper alimentation, lack of uniform protocols in*



*regard to initiation of oral/tube feeding. Particularly there was no attempt to calculate the caloric intake during NICU stay*

**Answer:** We agree. These variables were not collected in the database, and are now collected prospectively in the new, EPIPAGE II study, a prospective population-based cohort study in 25 regions of France in 2011, including 5000 very preterm children born alive. Associations between weight gain and neurodevelopmental outcome will be studied taking into account these parameters (age at the start of oral feeds, duration of intravenous nutrition, lack of uniform protocol,...). These limitations are now stated in the, fifth paragraph of discussion in revised manuscript ( 'Weaknesses' section):

“Moreover, how much fortifier was given could, unfortunately, not retrieved from either of the two databases, and thus some important variables such as overall caloric intake during neonatal intensive care unit stay could not be included in the analysis.” (Page 10, Line 31)

*2. It is an observational study hence associated deficiencies*

**Answer:** We agree, and weaknesses are addressed in discussion.

*3. No explanation for the mechanism. Although difficult to pin point authors should provide possible mechanisms for eg better bonding, better care given by parents*

**Answer:** We agree, and now address this point in revised discussion, fifth paragraph mother-child interaction (better bonding, better care given by parents) (Page 11, Line 4)

*There are a few minor typographical errors: page 10, line 47 LIKELY, Line 49 CAN*

**Answer:** these errors are corrected

## COMMENTS

*The main findings of the study are that in both independent cohorts of preterm infants studied, breastfeeding at discharge (continuation of breast feeding after discharge? ) was associated with a reduction in the risk for a suboptimal neurodevelopmental assessment at two or five years of age despite a higher risk for suboptimal growth (loss of one weight Z-Score) during neonatal hospitalization in these breastfed infants. They define these findings as “breastfeeding paradox” ,meaning that breast feeding in the NICU was associated with poor weight gain but continuation of breast feeding after discharge was associated with better neurodevelopmental outcome at 2 and 5 years of age in very preterm infants. These findings are of critical importance and provide strong evidence for breast feeding in extreme premature infants both during NICU stay and after discharge. It is agreed that taken all data from literature and current study there is a consistence benefit of BF on later neuro development. And it provides evidence to encourage mothers who wish to breast feed, ( Page 11 Lines 12-20 ...)*

However calling it a “Breastfeeding Paradox” is debatable. What is the paradox? Loss of weight by one Z score during hospital stay can be well explained independent of breast feeding. Suboptimal growth in extreme premature babies In the NICU is well recognized even in the formula fed infants . Such suboptimal growth is due to difficulties in delivering optimal calories to sick VLBW infants: illness, limitation of feeding, fluid intake and associated physiological constraints that affect nutritional intake in this population. However the beneficial effects of breast feeding on neurodevelopmental outcome are well recognized and the findings of this study confirm previous studies..

. My argument against the use of the term “Breast Feeding Paradox” is that it implies that breast feeding in NICU is THE CAUSE for low birth weight z scores. There are several factors that influence the weight growth in THE NICU which may adversely influence the growth of very preterm infants. As the investigators found that there was no association between NICU postnatal growth and developmental findings at 5 yrs.(p 8 line 55-60). Because nutrition was better in LIFT cohort . This again suggests that breast feeding is NOT the only cause low weight gain during the NICU stayThe study strengthens the concept that moms should be Advised to continue breast feeding of very premature babies after discharge from NICU.

**Answer:** We agree with Reviewer 2. First, the paradox may only be apparent. We therefore modified the title to ‘The apparent breast feeding paradox’ in the revised manuscript and we justify the term ‘apparent’ in the second paragraph of the discussion : “Nevertheless, this paradox is probably only an apparent paradox because weight gain during hospitalization is a poor predictor of the quality of growth, as it does not provide any insight into the changes in body composition”.

We also agree on the fact that the association between breastfeeding and loss of weight Z-score, does not prove causality, so breastfeeding may not be the only cause for the loss of weight Z-score in the NICU in the breast-fed infants. The association, however, is puzzling , as it was consistently found in both cohorts. Also, we believe a paradox exists since a better growth is generally associated with a better neurodevelopment in very preterm infants. In our study, we observe an association between breastfeeding and a better development, despite the loss of weight Z-score associated with breastfeeding. This indeed seems to be a paradox, since, even after adjusting for breastfeeding and propensity score, a loss of one Z-score is associated with suboptimal neurodevelopment in one cohort (LIFT cohort; adjusted OR: 1.28 (1.07-1.53); Table 5). This may, however, only be an apparent paradox, since weight gain a poor measurement of the quality of growth, as weight gain may not reflect fat free mass or brain growth. We therefore have initiated an ongoing study including assessment of body composition, and its relationship with neurodevelopment. We replace now “breastfeeding paradox” by “apparent breastfeeding paradox”

## VERSION 2 – REVIEW

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| <b>REVIEWER</b>        | Vidyasagar Dharmपुरi MD<br>Prof Emeritus<br>Dept Of Pediatrics<br>University Of Illinois at Chicago<br>Chicago ILL 60523<br>USA |
| <b>REVIEW RETURNED</b> | 14/02/2012  |

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| <b>THE STUDY</b>                 | Difficulties associated with retrospective data                   |
| <b>RESULTS &amp; CONCLUSIONS</b> | Authors have responded well to questions raised by the reviewers. |

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|                         | <p>In spite of their explanations two important questions remain.</p> <p>The first question is regarding the “Propensity Score”.</p> <p>In table #1 the investigators show significant differences between the breastmilk fed and non-breastmilk fed infants in terms of BWT, GA and in both EPIPAGE and LIFT groups. BWT, GA, Maternal Education, being higher or better in breast fed infants. These differences themselves may well explain why BF infants did well in later neuro-developmental score.</p> <p>When there is NO overlap between the groups why do the Propensity Score test? For readers it will be important to know the significance of the use of Propensity score.</p> <p>The Propensity Score by grouping these variables might indeed have masked the individual effect of these confounding variables (BWT and GA)</p> <p>The second question is regarding weight gain differences between breast milk fed and non-breast milk fed infants in both studies and the “apparent Paradox”.</p> <p>1. FIG 1 shows that where no differences in Z scores of wt. loss at discharge between the groups in EPIPAGE group but there was a difference in LIFT group</p> <p>2. Breastmilk fed babies in both groups had received fortifiers. As authors state in their response that indeed the LIFT group had received greater amounts (see author’s response).</p> <p>Is it possible that the observed better Neurodevelopment in breast milk fed infants is more a reflection of supplemental nutrition (fortifiers)? Therefore the observed “paradox” may be due to the effect of fortifiers than the associated wt. loss with BM feeding?</p> |
| <b>GENERAL COMMENTS</b> | <p>My main concern is the implication that better neurodevelopmental outcome is attributed to loss of weight during hospital stay (NICU) in breast milk fed infants (“The Paradox”). Such inference may lead to less attention to providing supplemental fortifies in the critical period of NICU stay.</p> <p>Authors may like to interpret the data and conclude in a more practical and positive way eg the importance of breast feeding and use of fortifiers to meet the nutritional needs during hospital stay.</p> <p>And encourage continuation of breast feeding with out the need of fortification, after discharge as they have already done.</p>   |

## VERSION 2 – AUTHOR RESPONSE

Answers to Reviewer

# BMJ.2011.001225.R1 entitled "The Breastfeeding paradox in very preterm infants"

We appreciate Reviewer 's insightful comments. In the following, excerpts from the Reviewer's comments are shown in italics, and immediately followed by our answers in Arial font.

Comment 1.1

The first question is regarding the Propensity Score.

In table #1 the investigators show significant differences between the breast milk fed and non-breast milk fed infants in terms of BWT, GA and in both EPIPAGE and LIFT groups. BWT, GA, Maternal Education, being higher or better in breast fed infants. These differences themselves may well explain why BF infants did well in later neuro-developmental score.

When there is NO overlap between the groups why do the Propensity Score test? For readers it will be important to know the significance of the use of Propensity score.

Answer: We observed a large overlap between the 2 groups, breastfed and not breastfed, in each cohort. We propose an additional analysis by creating matched pair of exposed and unexposed very preterm infants, created by their propensity score, and the outcomes of the two groups were compared. We created 386 pairs in EPIPAGE cohort (94% of 409 breastfed infants) and 271 pairs in LIFT cohort (97% of 278 breastfed infants). We present these results as a supplemental table. We think that this table helps readers to understand the significance of the propensity score.

#### Comment 1.2

The Propensity Score by grouping these variables might indeed have masked the individual effect of these confounding variables (BWT and GA)

Answer: It is why these variables were included as confounding factors in the multivariable models even if they are already included in the calculation of propensity score.

#### Comment 2.1

The second question is regarding weight gain differences between breast milk fed and non-breast milk fed infants in both studies and the «apparent Paradox».

1. FIG 1 shows that there were no differences in Z scores of wt. loss at discharge between the groups in EPIPAGE group but there was a difference in LIFT group

Answer: we agree with the reviewer, we did not observe significant difference in Z scores of wt. loss at discharge (fig3) or change in weight Z-score during neonatal hospitalization (table1) in EPIPAGE cohort. But not-breastfed group had a lower gestational age. After adjustment for gestational age or in matched pair comparison (supplemental Table) lost in weight Z-score during neonatal hospitalization is significantly less in not-breastfed group.

#### Comment 2.2

2. Breast milk fed babies in both groups had received fortifiers. As authors state in their response that indeed the LIFT group had received greater amounts (see author's response).

Is it possible that the observed better Neurodevelopment in breast milk fed infants is more a reflection of supplemental nutrition (fortifiers)? Therefore the observed «paradox» may be due to the effect of fortifiers than the associated wt. loss with BM feeding?

My main concern is the implication that better neurodevelopmental outcome is attributed to loss of weight during hospital stay (NICU) in breast milk fed infants («The Paradox»). Such inference may lead to less attention to providing supplemental fortifiers in the critical period of NICU stay.

Answer: We agree with the reviewer that better neurodevelopmental outcome is NOT attributed to loss of weight during hospital stay. In the first paragraph of discussion we indicated “ The observed improved neurodevelopment in spite of suboptimal initial weight gain could be termed the ‘apparent

breastfeeding paradox' in very preterm infants". Moreover, to be more clear, we inserted the following sentences "In conclusion, the neurodevelopment of premature infants is likely to benefit from feeding supplemented mother milk during hospital stay and unsupplemented mother's milk after discharge" and "Supplementation must be continued as long as possible according to the state of knowledge and this suggests also that more research in the conclusion

#### Suggestion

Authors may like to interpret the data and conclude in a more practical and positive way eg the importance of breast feeding and use of fortifiers to meet the nutritional needs during hospital stay. And encourage continuation of breast feeding without the need of fortification, after discharge as they have already done.

Answer: as suggested we inserted the following part of sentence at the beginning of the conclusion "In conclusion, the neurodevelopment of premature infants is likely to benefit from feeding supplemented mother milk during hospital stay and unsupplemented mother's milk after discharge"

#### VERSION 3 - REVIEW

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| <b>REVIEWER</b>        | Vidyasagar Dharmapuri MD<br>Prof Emeritus<br>Dept of Pediatrics<br>University of Illinois at Chicago<br>Chicago IL 60523<br>USA |
| <b>REVIEW RETURNED</b> | 29/02/2012  |

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| <b>GENERAL COMMENTS</b> | The authors have answered sufficiently well all my queries. |
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